REVIEW

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Ablation therapy for hepatocellular carcinoma: past, present and future perspectives

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Practice Points

- Hepatic tumor ablation continues to evolve toward providing maximum ablation effect with minimal damage to surrounding tissue.
- Percutaneous ethanol injection is a less commonly used ablation modality that is beneficial for lesions located near structures/vessels to be preserved.
- Radiofrequency and microwave ablation are the most commonly employed ablation modalities, and can be used in open surgery, minimally invasive surgery and percutaneous image-guided ablations.
- Irreversible electroporation is an emerging nonthermal ablation technology that preserves tissue architecture.
- Other emerging ablation modalities, such as high-frequency focused ultrasound, offer a means of performing thermal ablation without percutaneous insult.

SUMMARY Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and is most commonly found in the setting of liver cirrhosis. Treatment of HCC must consider both the tumors present, as well as the remaining dysfunctional liver that both hinders treatment and can produce additional HCC over time. Ablation is an evolving part of the multimodality treatment approach to HCC that can effectively destroy tumors while preserving surrounding liver parenchyma. New technologies have made ablation an indispensable tool in the treatment of all stages of HCC. This review presents the history, present technologies and future potential of ablation in the treatment of HCC.

Cancers of the liver represent a large, and growing, medical burden worldwide. Hepatocellular carcinoma (HCC), which accounts for 70–85% of all primary hepatic tumors, is the fifth most common cancer, and the third leading cause of cancer-related mortality worldwide [1,2]. Unlike many other common cancers, the prognosis for patients diagnosed with HCC remains bleak, and mean survival times following diagnosis

have not improved significantly over the last three decades. Paradoxically, the risk factors for developing HCC are well documented [3,4]: exposure to viral hepatitis (B and/or C) [5,6], chronic, heavy alcohol consumption [7,8], obesity [9,10], and/or aflatoxin ingestion [11] being the most common. Currently in the USA and, to an increasing extent, in western Europe, the pathogenesis associated with HCC is changing

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owing to the peaking incidence of viral hepatitis C infection, coupled with the increased incidence of obesity and nonalcoholic fatty liver disease, nonalcoholic steatohepatitis and non-alcoholic steatohepatitis-induced cirrhosis with subsequent progression to HCC [3,9,12].

Numerous factors contrive to limit improvements in prognosis for patients diagnosed with HCC. Most notably, development of the underlying liver pathologies that lead to hepatocyte transformation and progression to HCC usually occur over a period of decades [3,4]. This extended timeframe, in turn, makes tracking disease progression and early HCC detection particularly challenging. This task is further complicated by a (relative) lack of reliable HCC ‘biomarkers’ [13,14], an absence of familial patterns of disease development [15], and a lack of advanced diagnostic imaging systems for use in those regions in which HCC is most widespread [2,6]. The use of surveillance programs in high-risk populations and, in particular, the use of short-interval imaging surveillance, has been shown to result in ‘stage migration’ towards earlier diagnosis and improved overall survival. Early-stage diagnosis allows greater options in treatment, including locoregional therapies such as ablation [16].

Late detection and advanced HCC staging remain the most significant factors limiting treatment options for HCC patients. Additionally, medical therapy for HCC has not proven particularly beneficial. The reasons behind the failure of many ‘established’ cytotoxic compounds in treating HCC are varied, but most commonly relate to the role of the liver in drug metabolism. Complications associated with hepatic and systemic toxicity following systemic chemotherapy for HCC are in turn exacerbated by the hepatic cirrhosis that most commonly accompanies HCC [3,4]. Recently, the newer multikinase inhibitor, sorafenib, has been reported to provide a 2.7-month survival advantage over placebo in patients with advanced HCC [17–19]. Such poor performance of systemic chemotherapy mandates that HCC be treated with a multimodal approach. That is, treatment for HCC must address the tumor and take into consideration the remainder of the dysfunctional liver, with possible occult tumors present at a subclinical size.

Resection, either in the form of partial hepatectomy or liver transplant, provides the best chance for disease-free and overall survival in patients with HCC [20–22]. Surgical resection, however, is often prohibited by the poorly

functioning cirrhotic liver, moderate-to-severe portal hypertension, the presence of extra- or intra-hepatic metastases and/or the location of the tumor within the liver. Resection of the tumor also removes noncancerous tissue, and many patients with advanced cirrhosis cannot tolerate further loss of functioning liver parenchyma as a result of resection. Even after successful surgical resection, long-term survival is often limited by recurrence of HCC remote to the original tumor, in the residual, diseased liver [21,23]. Transplant provides a much-improved long-term outcome, at least in terms of HCC recurrence, since the entire cirrhotic liver is removed, but only 9–16% of patients with HCC fall within the Milan criteria, making transplant unavailable to the vast majority of HCC patients [20,22,24]. Limitations in organ availability, underlying disease pathology, and overall medical fitness of the patient prior to transplant, make transplantation unavailable to the majority of those who fall within the subset of patients diagnosed with cirrhosis and/or HCC.

Regional therapy for HCC, in the form of either transarterial chemoembolization [25] or transhepatic localized tissue destruction (ablation) [26,27], provides an opportunity to treat HCC more aggressively than systemic therapy alone and offers the advantage of leaving remnant, noncancerous liver tissue in place. An additional benefit to regional therapy exists for those patients who fall within the Milan criteria and are considered for transplant. Under current regulations, exception points are provided for patients with HCC, which elevate them on the transplant list and increase the odds of receiving a donation. After resection, exception points are lost, but with regional therapies patients retain their exception points and remain higher on the transplant list. Regional therapies also retard the growth of lesions, or halt it completely in the case of ablation, reducing the likelihood of progression outside the size limits of the Milan criteria and subsequent dropout while awaiting a transplant.

In situ tumor destruction has undergone many generations of change since its inception more than 150 years ago, and new technology holds the promise of additional benefits for HCC patients. The aim of this review is to provide a concise history of ablation, an examination of currently available technology and a look at ongoing, future developments for the treatment of HCC through ablation.

Cryoablation

The use of cold in surgical applications (cryosurgery) dates to the mid-19th century and the practice has developed subsequently from a concentration on topical, or easily accessible sites, to applications in treating lesions located deep within visceral tissue [28]. Initial progress in the use of cryosurgery in liver surgery was significantly hindered by the inability to visualize lesions deep within the organ [29]. This limitation was largely overcome with the introduction of intraoperative ultrasound in the 1990s and accompanying advances in cryotherapy technology. Effectively, this technology allowed for accurate lesion identification, guided cryoprobe placement and ‘real-time’ monitoring during the freezing process [29].

Cryotherapy relies on the insertion of a cooling rod (probe), equipped with liquid nitrogen, argon or other coolants into the mass to rapidly freeze the tumor. The probe is then removed and the frozen tissue is allowed to thaw slowly *in situ*. Typically, two freeze–thaw cycles are performed sequentially to maximize cell death. With the advent of better cryosurgery probes and intraoperative ultrasound, cryotherapy, using both open [30] and laparoscopic [31] approaches, became a more common means to treat liver lesions and is reported as an effective and safe therapy with complication rates comparable with those associated with resection. Although minimally invasive techniques have been developed

for cryoablation [30], the emergence of alternative ablation technologies has made cryoablation largely the preserve of niche applications. Additionally, an unfavorable complication profile, including potential ‘cracking’ of the liver, bile leaks, bleeding and ‘cryoshock’, has led to cryoablation falling out of favor with the majority of liver surgeons.

Percutaneous chemical injection

The most common nonthermal method of *in situ* tumor destruction involves direct injection of chemicals into the tumor [32,33]. Of these chemicals, the most widely used and reported in the treatment of HCC are ethanol and acetic acid (Table 1). The success of this method of tumor destruction relies as much on the pathological characteristics of HCC arising in the setting of underlying hepatic cirrhosis, as on the chemical properties of ethanol and acetic acid. In the setting of hepatic cirrhosis, the tumor is (usually) surrounded by a pseudocapsule, is highly vascularized and is relatively pliable compared with the remaining fibrotic, nontumorous liver tissue. As such, infiltrated chemicals are prone to disperse within the tumor, yet remain within the pseudocapsule, largely sparing the nontumor tissue while increasing the (injected) chemical concentration within the tumor.

As with other ablation modalities, the use of percutaneous ethanol injection (PEI) to treat HCC grew exponentially with the emergence of

Table 1. Highlights from selected articles for percutaneous ethanol injection treatment of hepatocellular carcinoma summarizing patient numbers, tumor characteristics and response rate.

Study (year)	Type of study	Patients (group, n)	Tumor characteristics (mean size, mm)	Complete response rate (assessment modality, %)	Survival	Study conclusions	Ref.
Branco <i>et al.</i> (2009)	Retrospective PEI prior to transplant	62 (PEI) 35 (control)	All HCC within Milan criteria	64.3 (pathologic)	Not evaluated	PEI is safe and effective prior to liver transplant	[38]
Castroagudin <i>et al.</i> (2005)	Retrospective PEI prior to transplant	27 (PEI)	All HCC within Milan criteria (30.8 ± 12.9)	65 (pathologic)	Not evaluated	PEI achieves significant necrosis in HCC awaiting transplant	[39]
Shiina <i>et al.</i> (2012)	Retrospective Single institution	685 (PEI)	All HCC (28.3 ± 14.7)	98.5 (radiographic)	49% 5-year survival	Excellent results; however, newer techniques may perform even better	[44]
Ebara <i>et al.</i> (2005)	Retrospective Single institution	270 (PEI)	All HCC (≤30)	100 (radiographic)	60.3% 5-year survival	PEI is reliable and safe	[45]

HCC: Hepatocellular carcinoma; PEI: Percutaneous ethanol injection.

improved transcutaneous and operative ultrasound-guided techniques. Early studies by Shiina *et al.* and Livraghi *et al.*, demonstrated successful tumor ablation with ethanol injected percutaneously, using ultrasound guidance [34,35]. Although small, both studies contained biopsy results for at least some patients, either through needle biopsy or operative resection, demonstrating a high degree of tumor necrosis [34,35]. Following PEI, desiccation and nonselective protein denaturation occurs, leading to cell death. Unlike thermal ablation approaches, PEI (typically) requires four to eight sessions and is performed over a period of 2–6 weeks. To date, the largest body of data for PEI has come from Asian literature, and several studies have compared and contrasted outcomes using PEI with those of other approaches [32,33,36]. The results of many of these studies were published in the 1980–1990s, reporting favorable outcomes in those patients who could not undergo resection of their HCC, with PEI proving particularly effective for small (≤ 3 cm) nodular tumors arising in the cirrhotic liver. One Japanese study reported complete necrosis in 13 out of 18 resected tumors having undergone anywhere from one to nine PEI sessions [37]. Similarly, studies examining explanted livers treated with PEI prior to transplant have demonstrated complete necrosis of approximately 65% of small HCC [38,39]. Western series report similar data, with some patients undergoing up to 14 sessions [40]. Complications rates for PEI are low in one western series, and corroborate several eastern series [37,40,41].

Despite its safety and 5-year survival rates being reported as high as 32–59% in selected PEI-treated patients, PEI is rarely used now as the sole ablation therapy to treat HCC. The reasons for the fall in popularity of PEI include reports of tumor seeding of the abdominal wall, the uncertainty of complete ablation and the (relatively) long treatment times required. This, in turn, leads to potentially high recurrence rates (up to 33% in lesions < 3 cm and 43% in lesions ≥ 3 cm) [33,42,43]. One study reporting long-term results of PEI commented that radiofrequency ablation (RFA) has largely replaced PEI as the primary ablation modality [44]. However, for patients with peripheral lesions near the viscera or diaphragm, who cannot undergo either resection or laparoscopic ablation, PEI remains a valuable tool to percutaneously treat these select lesions [45].

An alternative to PEI involves the percutaneous injection of 50% acetic acid (percutaneous

acetic acid injection [PAI]). In addition to affecting cell toxicity, PAI can also act to penetrate and destroy intranodule septa, thus providing more widespread tumor cell destruction. As a result, PAI can often be performed as easily as PEI, yet routinely requires fewer treatment sessions. Using PAI, Fartoux *et al.* reported complete tumor destruction in 76% of patients with an average of 1.6 sessions [46]. However, as with PEI, PAI is associated with high recurrence rates of up to 34% at 2 years. More recently there have been two meta-analyses comparing RFA with either PEI alone, or with PEI or PAI. In 2009, Orlando *et al.* found RFA to be superior to PEI in terms of overall survival, cancer-free survival and local recurrence rates [36]. A separate meta-analysis by Germani *et al.* in 2010 reported that for all outcomes PAI did not differ significantly from PEI, and both approaches were inferior to RFA [47]. However, when considering only tumors ≤ 2 cm, PAI and RFA outcomes were similar, suggesting the role for PAI in treating this group of HCC patients may need to be more thoroughly evaluated [47].

Radiofrequency ablation

RFA is a thermal ablation modality that relies on tissue heating (hyperthermia) to induce tumor destruction. Despite RFA technology being introduced clinically in the late 1970s, US FDA approval for RFA application in liver lesions was not granted in the USA until 1997. Since then, enthusiasm for RFA has propelled this technology to its current status as the most widely used thermal ablation technology for treating liver cancers, both primary and metastatic, in the world [48–51]. RFA technology is based on the interaction of an alternating electric current with tissue, during which ions become agitated by the passing through of high-frequency radiowaves (460–480 kHz) [49]. The subsequent production of frictional heat is conducted into the tissue in a predictable manner leading to coagulative necrosis [49,50]. The current density generated is determined by the current concentration created between pads on the patient's skin and the tips of the ablation probe that are inserted directly into the tumor; the high current concentration at the tip leads to tissue heating.

None of the restrictions associated with cryoablation in treating tissue (cryoshock and bleeding secondary to cracking of the liver when freezing) are evidenced with approaches that heat the tissue to elicit cellular destruction. However, the

use of RFA to treat HCC is not without its own unique set of challenges. Most notably, as with any electrical heating system, the most important factor affecting current flow is impedance. In this respect, a significant challenge in the use of RFA is that tissue impedance changes as the tissue undergoes coagulation and desiccation associated with heating. As impedance increases in the ablated tissue, so the electrical current flow will change to continue along the 'path of least resistance'. In the liver this phenomenon most commonly results in blood vessels in close proximity to the site of ablation acting as an electrical 'sink' and conducting the current away from the ablation site. Similarly, as the tumor becomes heated, these blood vessels can also act as thermal sinks to carry heat away from the site of ablation. As a result of electrical and thermal sinks, the ablation shape and volume can become difficult to predict, increasing the possibility of incomplete ablation and subsequent tumor recurrence. RFA is therefore more effective with a vascular inflow occlusion technique such as the Pringle makeover. In addition, high temperatures at the tip of the ablation probes can lead to charring of the tissue, an event that dramatically increases local impedance, significantly diminishes current through the probe and may lead to excessive heating of the probe [49]. Finally, the presence of this heat sink near large hepatic vessels during RFA can increase the patient's core temperature. Collectively these limitations mean RFA is most typically employed to ablate hepatic tumors ≤ 5 cm [48].

Long-term outcomes of RFA as treatment for HCC have been published by several groups (Table 2). Shiina *et al.* present excellent results at 5 and 10-year follow-up after ablation of HCC [52]. They achieved a complete ablation rate of 99.4% with a local recurrence rate of only 3.2% at 10 years. Regional recurrence and extrahepatic metastatic spread remained a significant cause of mortality, with 74.8% of patients having regional or metastatic disease at 5 years [52]. Francica *et al.* looked at patients undergoing RFA for solitary HCC ≤ 3 cm [53]. Their major complication rate of 2.2% and 5-year survival of 64% corroborate other published series [53].

A Cochrane review from 2004 specifically examined RFA against other interventions for HCC and identified two randomized clinical trials that met inclusion criteria [54]. In the first trial, percutaneous RFA was compared with PEI for patients with small HCC (< 5 cm) [54,55]. A

total of 104 patients (144 tumors) were randomized with adequate generation of allocation sequence and concealed allocation, but without blinding. Survival rates at 2 years postprocedure (mean follow-up: 22 months) were 98% in the RFA group and 88% in the PEI group (hazard ratio: 0.20; 95% CI: 0.02–1.69; $p = 0.14$) [55]. Recurrence-free survival rates were 64% in the RFA group and 43% in the PEI group (hazard ratio: 0.48; 95% CI: 0.27–0.85; $p = 0.01$) [55]. No procedure-related deaths, hemorrhage, infections, needle-tract seeding or hepatic failure were observed in either group, and data on other outcomes were not available.

In the second trial, percutaneous RFA was compared with percutaneous microwave ablation (MWA) for small HCCs (< 4 cm) [56]. This trial is described as randomized, but the generation of the randomized sequence is unclear and performed without blinding for 72 patients with 94 hepatic tumor nodules to percutaneous RFA or percutaneous MWA [56]. Overall survival rates were not able to be calculated because the published data were based on tumor nodules and not on the individual patients. During follow-up (mean: 18 months; range: 6–27 months) residual tumor was detected in 12% of the RFA-treated tumors and 24% of the MWA-treated tumors ($p = 0.20$; log rank test) [56]. No deaths or life-threatening events were observed during the trial in either group. One major complication was observed in the RFA group and four in the percutaneous MWA but this difference did not reach statistical significance ($p = 0.36$) [56]. Overall, the authors of the Cochrane review assert that an investigation of treatments for HCC in randomized clinical trials is possible, necessary, and should be demanded to make an unbiased assessment of therapeutic strategy before implementation in clinical practice [54]. Furthermore, they contend that in order to gain a higher level of external validity, trials involving RFA should be conducted as multicenter trials as percutaneous interventions are strongly affected by the individual experience of the investigator [54].

More recently, two meta-analyses have been published addressing RFA use in HCC treatment [57,58]. The first was an overview of the evidence-based management of HCC by Salhab and Canelo and included four randomized, controlled trials of RFA for local therapy in a meta-analysis of studies published from 2005 to 2010 [57]. These four trials were not homogenous in terms of population or end points (primary and secondary).

Table 2. Highlights from selected articles for radiofrequency ablation treatment of hepatocellular carcinoma summarizing patient numbers, tumor characteristics and response rate.

Study (year)	Type of study	Patients (group, n)	Tumor characteristics (mean size, mm)	Complete response rate (assessment modality, %)	Survival (%)	Study conclusions	Ref.
Shiina <i>et al.</i> (2012)	Retrospective Single institution	1170 (RFA)	All HCC (25.4 ± 10.4)	99.4 (radiographic)	60.20 5-year survival	RFA is potentially locally curative	[52]
Huang <i>et al.</i> (2010)	Randomized controlled trial RFA vs resection	230 (total) 115 (RFA)	All HCC Solitary tumor <30 (n = 45) Solitary tumor >30 (n = 44) Multiple tumors (n = 26)	100 (radiographic)	54.78 5-year survival (RFA) 75.65 5-year survival (resection)	Resection may provide better survival and lower recurrence than RFA within Milan criteria	[63]
Feng <i>et al.</i> (2012)	Randomized controlled trial RFA vs resection	168 (total) 84 (RFA)	All HCC (24 ± 6 RFA group)	94 (radiographic)	67.20 3-year survival (RFA) 74.80 3-year survival (resection)	RFA is equivalent to resection in small HCC	[64]

HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation.

The end points of the meta-analysis included the complete response rate at 1 year, overall survival at 3 years and adverse complications. The odds ratio for complete response at 1 year showed equivalence for RFA compared with PEI (odds ratio: 1.238; 95% CI: 0.872–1.759; $p > 0.005$) [57]. The heterogeneity among the four trials was significant when the complete response rate was considered as an end point (Q : 17.43; $p = 0.001$) but not in regard to overall survival at 3 years or regarding adverse events [57]. Conversely, RFA was reported to be superior to PEI relative to overall survival at 3 years (odds ratio: 1.68; 95% CI: 1.206–2.391; $p = 0.002$) [57]. When adverse events were considered, there were no significant differences between HCC patients treated with RFA versus PEI (odds ratio: 1.199; 95% CI: 0.571–2.521; $p = 0.632$) [57]. Furthermore, a secondary subgroup analysis by tumor size was unable to be performed owing to the lack of uniformed data from the studies included in the meta-analysis.

The second systemic review and meta-analysis examined survival and disease recurrence for HCC patients treated using RFA between January 2000 and November 2010 [58]. Of the 43 articles considered, including 12 randomized, controlled trials, the majority ($n = 30$) reported RFA was employed for unresectable HCC, often in combination with other treatments including PEI, transarterial chemoembolization and/or resection. Among the eight nonrandomized studies for patients within the Milan criteria, none demonstrated significant differences in overall

survival rates when comparing RFA with resection [58]. However, patients undergoing resection had significantly lower local recurrence rates (0–10 vs 7–24% for ablation-site recurrence, and 33–51 vs 28–68% for recurrent intrahepatic disease), and higher disease-free survival rates [58]. Median disease-free survival rates at 1, 3 and 5 years in the resection group were 80–83, 47–64 and 22–38%, respectively [58]. The corresponding rates for the ablation group were 78–83, 36–59 and 17–25% [58]. There were also eight nonrandomized studies that met inclusion criteria that examined RFA versus resection and included patients outside of the Milan criteria. Median overall survival rates at 1, 3 and 5 years in the RFA groups were 78–98, 33–94 and 20–75%, respectively, as compared with the corresponding rates in the resection group of 75–97, 64–93 and 31–81%, respectively [58]. The ablation-site, intrahepatic and extrahepatic disease recurrence rates were 3–15, 25–29 and 12–21%, respectively, for the RFA group, compared with 0–2, 28–37 and 13%, respectively, in the resection group [58]. The authors conclude that RFA provides a valuable treatment option for patients with unresectable HCC and improves survival in those previously considered to have advanced disease.

In comparing RFA with PEI for the treatment of unresectable HCC, five randomized controlled trials were included in the meta-analysis, which showed patients treated with RFA had better 1- and 3-year overall survival than those treated with PEI [58]. RFA was associated with significantly

better disease-free survival rates at 1 and 3 years: 74–86 and 37–43%, respectively, versus 61–77 and 17–21%, respectively, in the PEI group [58]. Disease recurrence rates at the ablation site were significantly lower in the RFA group than in the PEI group (2–14 vs 11–35%) [58]. From this the authors conclude that overall and disease-free survival rates continue to improve, despite an increase in the size and number of tumors treated.

In more recent reports, clinicians have begun utilizing RFA and other ablative modalities to treat select patients presenting with resectable HCC with favorable outcomes [59–62]. Several randomized trials have compared surgical resection with RFA for HCC ≤ 3 cm. Huang *et al.* found superiority of resection over ablation in terms of overall and disease-free survival with a 5-year overall survival of 75.65 and 54.78%, respectively [63]. Feng *et al.* also randomized patients to either resection or ablation for small HCC and found no statistically significant difference in survival for their patients [64]. Pompili *et al.* performed a large multicenter survey of resection versus ablation and found no difference in survival, but a higher rate of local recurrence after ablation [65]. These studies support the practice of elective ablation for early-stage HCC.

Microwave ablation

As RFA was being adopted in the USA in the early 2000s, so the first cases of treating liver tumors using MWA began to be reported [66]. Unlike RFA, no current passes through the patient during MWA since the energy is emitted via the ablation antenna as microwaves. Similar to commercial microwave applications, as microwaves pass through tissue, a rapid alignment–realignment of dipolar molecules (e.g., water) occurs, leading to heat generation and coagulative necrosis. Unlike RFA, this means the alignment–realignment of water molecules is (essentially) uniform within the field in which the microwaves are transmitted (the ‘near field’). This, in turn, enables the performance of a more predictable, uniform ablation, as MWA is less susceptible to local tissue factors such as proximity to large blood vessels and associated electrical–thermal sink effects [49,51,67]. Outside the microwave near field, however, heat conduction will occur, and the possibility of a thermal sink effect owing to the conductivity of blood vessels in perfused tissue exists within the conduction zone. Since complete tumor destruction is guaranteed if the tumor is enveloped by

the microwave near field zone, optimal ablation needle placement is critical in determining MWA outcome.

Currently, MWA is employed at two distinct frequencies: 915 MHz (FDA approved in 2003) and 2.45 GHz (FDA approved in 2006). These wavelengths have specific physical properties with regard to tissue permeability and antenna design. The 915 MHz system generally allows for deeper tissue penetration of the microwaves, and as a result, a generally lower energy density within the microwave field, necessitating longer ablation times. While increasing the power can shorten the ablation time, the amount of energy that can be delivered remains limited by the antenna and cable design. At high-energy levels, the energy loss in the system and the charring of the antenna tip caused by excessive heating diminishes the efficacy of the energy delivery [48]. Conversely, the 2.45 GHz MWA system has less tissue penetration, but a much higher energy density within the field, making it possible for a larger ablation to be achieved with a single antenna [48]. Both systems should be utilized in a complementary fashion, as smaller lesions near vital vascular structures are more appropriately treated with the 915 MHz system, and larger lesions are more efficiently ablated with the 2.45 GHz system.

Boutros *et al.* performed a recent review of the literature and critical analysis of microwave coagulation therapy for hepatic tumors with the primary purpose of evaluating the presently available data for MWA, and assessing the level of evidence to support clinical use [68]. The review was limited to published studies in the English language, at least 30 patients/study and MWA employed to treat HCC or colorectal hepatic metastases (CRHM). Outcomes of interest included patterns of local recurrence, complications and survival outcome of MWA, including assessment of the Asian experience (using the 2.45 GHz device) and the American experience (using the 915 MHz device). The authors conclude that while randomized clinical trials comparing RFA with MWA for hepatic ablation are lacking, their review (based on level 2 data) supports the position that MWA may be optimal when larger necrosis zones and/or ablation of multiple lesions are the objective [68]. MWA, as with other ablation modalities, shares a high rate of regional recurrence in HCC, a factor likely to be due to the multicentricity of the disease process and unrelated to the ablation modality chosen.

In the eastern experience, five studies were reviewed and all studies demonstrated favorable responses (89–94% complete radiographic response on first follow-up imaging study) and long-term survival (3-year survival; 66–73%) of HCC following MWA [69–73]. While complication rates of 1.3–7% were reported, a 5-year survival rate of 51 and 56.7% was reported in two separate studies. One study was reviewed regarding CRHM in 52 patients that underwent percutaneous MWA, open MWA or MWA in combination with hepatic resection, and cumulative 5-year survival rates for these different treatment groups were 20, 24 and 24%, respectively [74].

In the American experience, US multicenter Phase I and Phase II trials have been conducted using the 915 MHz MWA system (Table 3) [66,75]. In the Phase I clinical trial, ten patients with CRHM or HCC liver lesions were treated with MWA before elective surgical resection of the ablated tumor [75]. In these studies, mean maximal tumor diameter treated was 4.4 cm and mean ablation diameter was 5.5 cm (average ablation volume was 50.8 cm³) [75]. In the Phase II clinical trial using clustered microwave antennae, 87 patients underwent a total of 94 MWA procedures, of which 42 ablations (45%) were performed open, 7(7%) laparoscopically and 45 (48%) percutaneously, with a mean tumor size of 3.6 cm, and single antenna ablation volumes of 10 ml (mean clustered antennae ablation volume of 50.5 ml) [66]. Following treatment, local recurrence at the ablation site occurred in 6 (2.7%) instances, and regional recurrence occurred in 37 (43%) patients [66]. With a mean follow-up of 19 months, 41 (47%) patients were alive without evidence of disease [66]. There were no procedural-related deaths and overall mortality was 2.3% [66].

In addition to these multicenter trials, Martin and colleagues published a single-center, prospective Phase II trial evaluating the safety and efficacy of MWA of hepatic tumors over a 5-year period [76]. In their series, 100 patients underwent a total of 270 ablations for hepatic malignancies of which the most common tumor types were CRHM (50%) and HCC (17%). The majority of patients (53%) underwent combination hepatic resection and MWA with 38% undergoing ablation alone and 9% undergoing additional organ resection. Within the study group the median tumor size was 3.0 cm (range: 0.6–6.0 cm), the median number of tumors was two (range: 1–18) and median total ablation time was 13 min (range: 5–45 min). Overall, 90-day mortality was 0% and morbidity was 29%. Median follow-up was 36 months with five patients (5%) identified as having incomplete ablations, two (2%) having local recurrence at the ablation site, and 37 (37%) having developed intrahepatic recurrence at nonablated sites. Finally, a planned matched comparison of MWA and RFA with regards to ablation time, operative time, and hospital charges was performed. The two groups were evaluated for ablation success, ablation recurrence and ablation time, all of which were significantly improved in the MWA group. Ablation and operative times were significantly shortened in the MWA group, primarily related to the ability to do simultaneous ablations with multiple probes. The reduced ablation and operating room times translated to improvements in operating room charges, and operating room fixed direct charges (p = 0.02) [76]. The authors concluded that MWA of hepatic tumors is a safe and effective method for treating unresectable hepatic tumors, with a low rate of local

Table 3. Highlights from selected articles for microwave ablation treatment of hepatocellular carcinoma summarizing patient numbers, tumor characteristics and response rate.							
Study (year)	Type of study	Patients, n	Tumor characteristics (mean size, mm)	Recurrence (%)	Survival	Study conclusions	Ref.
Iannitti <i>et al.</i> (2007)	Prospective Phase II trial	87 (total) 23 (HCC)	Mixed tumor types (36, range: 5–90)	2.7 local recurrence	61% of HCC patients NED at mean follow-up 19 months	MWA is a safe and effective technology	[66]
Martin <i>et al.</i> (2010)	Prospective Phase II trial	100 (total) 17 (HCC)	Mixed tumor types (30, range: 6–60)	5 incomplete ablation 2 local recurrence	Median survival HCC patients (41 months)	MWA is safe and effective with low local recurrence	[76]
Swan <i>et al.</i> (2013)	Retrospective Single institution	54 (HCC with cirrhosis)	All HCC (median: 26, range: 5–85)	5.9 incomplete ablation 2.9 local recurrence	58.8% 2-year survival	MWA is safe in setting of cirrhosis	[27]

HCC: Hepatocellular carcinoma; MWA: Microwave ablation; NED: No evidence of disease.

recurrence, and noted that their data further confirm the initial collaborative Phase II trial evaluation of MWA [66]. Most surgical MWA are performed laparoscopically, achieving lower procedure related morbidity. One study, looking at 54 consecutive patients undergoing MWA used a minimally invasive technique in 94.5% of cases [27].

To date, no randomized, controlled clinical trials have been performed to directly compare outcomes for those treated with RFA versus MWA. However, a Phase III trial, sponsored by the Chinese University of Hong Kong, is currently recruiting patients to evaluate the effectiveness of MWA compared with RFA for treatment of localized unresectable HCC (ClinicalTrials.gov, identifier NCT01340105 [101]). Efficacy of treatment outcome will be assessed by complete tumor ablation rate at 1 month, recurrence rate and survival time. Safety of the procedures is also compared between the two treatment arms, and the study is anticipated to be complete with follow-up results expected in 2016. The current global trend is an increasing use of MWA and decreased reliance on monopolar RFA.

Percutaneous laser ablation

A less well-studied method of thermal ablation is percutaneous laser ablation (PLA). Needles are introduced percutaneously under image guidance into the tumor in arrays of 2–4. Optical fibers are passed through the needles and then the needles are retracted a short distance to expose the tip of the optical fiber for energy delivery. Near-infrared light is emitted and absorbed by tissues in proximity to the fibers, creating zones of coagulative necrosis in a fashion similar to microwave. There is no electricity transmitted, so ‘electrical-sink’ is not a risk as it is for RFA. Since the light energy is absorbed within a short radial distance from the optical fiber, planned ablations can theoretically be performed near vulnerable structures, with appropriate attention to precise needle placement and ablation times. Results for PLA in HCC are good for small lesions, but still inferior to the well-tested results of both RFA and MWA [77,78]. Pacella *et al.* report an initial complete ablation rate of only 78.2%, which is below that accepted for both MWA and RFA [78]. For tumors less than 2 cm in size, initial complete ablation rate was 85.1%. Overall 3- and 5-year survival in this study were 61 and 34%, respectively [78]. PLA is actively being researched, but with the rapid growth of MWA and newer

technologies such as irreversible electroporation and high-frequency focused ultrasound (HIFU), it is unlikely to become a major modality for hepatic ablation.

Irreversible electroporation

One of the newer modalities for solid tumor ablation is irreversible electroporation (IRE). In the IRE system, a high voltage (1500–2000 V/cm) electrical potential difference is pulsed in 80 ms bursts across the target tissue in a bipolar fashion. In doing so, pores are induced in the lipid bilayer of cells that remain even after the ablation stimulus is removed. The damaged cell membrane leads to compromised cell functionality and the induction of programmed cell death (apoptosis). In comparison to cryoablation, RFA and MWA, IRE is unique in that it is a nonthermal form of tissue destruction and, as such, may offer unique advantages to thermal approaches [79–82]. Preclinical studies using a swine liver model suggest IRE is not affected by heat sink. Since the site of action of IRE is the integrity of the cell membrane, a cellular elements of tissue are more resistant to the effects ablation. As a result it seems highly likely that IRE can be performed safely in regions adjacent to complex or fragile structures (e.g., bile ducts) without the risk of the same degree of damage that might be expected with thermal ablation modalities such as cryoablation, RFA or MWA [83–85]. However, it should be noted that the IRE system requires considerably longer ablation times than both RFA or MWA; the system requires the placement of a minimum of two, and up to six, ablation electrodes; and the maximum size of tumors that can be ablated is (generally) less than that which can be achieved using a single RFA or MWA application.

The most important study to date regarding IRE for liver tumors is trial NCT01078415 [102], a prospective, multicenter study to evaluate the safety and efficacy of IRE as first-line treatment in biopsy-proven, early stage HCC [86]. In this series, Lencioni *et al.* report a complete response in 23 out of 29 (79%) tumors by modified Response Evaluation Criteria in Solid Tumors (mRECIST) as assessed by an independent, central, blinded review. The authors reported no 30-day mortality in the series, major complications were rare and included only one case of hemothorax related to electrode placement and one case of transient hepatic decompensation with spontaneous resolution.

Clinical experience with IRE is growing, and its role in the treatment of malignancy evolving. Experience with pancreas ablation demonstrates ablations can be safely performed enveloping major vascular structure with low morbidity rates [87–89]. As an ablation technique with the ability to spare surrounding structures from thermal destruction will allow tumors near hepatic pedicles to be more effectively ablated than current thermal ablation techniques, reducing incomplete ablation rates while preserving the function and integrity of vascular and biliary structures.

High-intensity focused ultrasound

HIFU, while employed in China and on an experimental basis in Europe for the treatment of hepatic lesions, remains in the early stages of progressing toward clinical use in the USA. Unlike RFA, MWA and IRE, which all employ energy in the electromagnetic spectrum, HIFU utilizes ultrasonic waves to generate lethal tissue temperatures within a highly confined, predetermined area. With the aid of ultrasound or MRI, HIFU can produce highly accurate tumor ablations transcutaneously. This ‘trackless’ ablation eliminates the potential for collateral tissue damage from needles or antennae [90]. In addition, the heat produced by HIFU is generated quickly enough to marginalize the effect of perfusion removing heat from tissues [90]. This eliminates the heat sink effect that decreases effectiveness of other ablation approaches around large blood vessels.

Early data report promising results using HIFU to treat HCC. Zhang *et al.* treated 39 patients with HIFU for HCC ranging in size from 1.5 to 22 cm [91]. Complete ablation was attained in 50% of tumors after a single HIFU session without major blood vessel injury, even in tumors adjacent to major vascular pedicles [91]. Although general or epidural anesthesia is required for this procedure, the ability to accurately ablate tumors without the use of needles or incisions makes HIFU a potentially attractive treatment modality within the high-risk cirrhotic cohort.

There is a paucity of experience with HIFU in the treatment of hepatic malignancy in western centers, and further study will help to delineate

its role within the treatment paradigms for HCC. Development of a laparoscopic HIFU probe is under way, which, when combined with the benefits of intraoperative ultrasound, may allow precise treatment of liver tumors with minimal collateral damage to liver parenchyma.

Conclusion & future perspective

Treatment for early-stage HCC with ablation has become the standard of care, with results equivalent to resection [59,61,92]. Advances in both thermal and nonthermal ablation technologies continue to expand the role of ablation and improve outcomes associated with higher stages of HCC. MWA and RFA have been demonstrated to provide excellent results, with low local recurrence rates and excellent morbidity rates. Limitations in these thermal ablations, such as the anatomical constraints associated with major portal pedicles, may be overcome by nonthermal ablation modalities such as IRE. Advancements in intraoperative imaging guidance, with the introduction of novel 3D targeting systems, will allow greater accuracy in needle placement, further reducing incomplete ablation rates and making ablation more accessible to patients outside of tertiary institutions [93,94]. Additional testing of HIFU may allow effective ablation without skin penetration of any kind. For more advanced disease, the combination of ablation with other modalities of treatment, such as transarterial chemoembolization, has reduced the local and regional recurrence rates and improved overall and disease-free survival [95]. Hepatic ablation has evolved to occupy the forefront of multimodality treatment options available for HCC, and future technologies will make ablation more effective to further improve patient outcomes.

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References

- 1 El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 132(7), 2557–2576 (2007).
- 2 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J. Clin.* 61(2), 69–90 (2011).
- 3 Cabibbo G, Maida M, Genco C, Antonucci M, Camma C. Causes of and prevention strategies for hepatocellular carcinoma. *Semin. Oncol.* 39(4), 374–383 (2012).
- 4 Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 379(9822), 1245–1255 (2012).

- 5 Arzumanyan A, Reis HM, Feitelson MA. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. *Nat. Rev. Cancer* 13(2), 123–135 (2013).
- 6 El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 142(6), 1264–1273.e1 (2012).
- 7 Altamirano J, Bataller R. Alcoholic liver disease: pathogenesis and new targets for therapy. *Nat. Rev. Gastroenterol. Hepatol.* 8(9), 491–501 (2011).
- 8 Mckillop IH, Schrum LW. Role of alcohol in liver carcinogenesis. *Semin. Liver Dis.* 29(2), 222–232 (2009).
- 9 Sun B, Karin M. Obesity, inflammation, and liver cancer. *J. Hepatol.* 56(3), 704–713 (2012).
- 10 White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin. Gastroenterol. Hepatol.* 10(12), 1342–1359.e2 (2012).
- 11 Liu Y, Chang CC, Marsh GM, Wu F. Population attributable risk of aflatoxin-related liver cancer: systematic review and meta-analysis. *Eur. J. Cancer* 48(14), 2125–2136 (2012).
- 12 Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J. Hepatol.* 56(6), 1384–1391 (2012).
- 13 Bertino G, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellular carcinoma serum markers. *Semin. Oncol.* 39(4), 410–433 (2012).
- 14 Sengupta B, Siddiqi SA. Hepatocellular carcinoma: important biomarkers and their significance in molecular diagnostics and therapy. *Curr. Med. Chem.* 19(22), 3722–3729 (2012).
- 15 Nishida N, Kudo M. Recent advancements in comprehensive genetic analyses for human hepatocellular carcinoma. *Oncology* 84(Suppl. 1), 93–97 (2013).
- 16 Santi V, Buccione D, Di Micoli A *et al.* The changing scenario of hepatocellular carcinoma over the last two decades in Italy. *J. Hepatol.* 56(2), 397–405 (2012).
- 17 Carr BI, Carroll S, Muszbek N, Gondek K. Economic evaluation of sorafenib in unresectable hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 25(11), 1739–1746 (2010).
- 18 Llovet JM, Ricci S, Mazzaferro V *et al.* Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 359(4), 378–390 (2008).
- 19 Ranieri G, Gadaleta-Caldarola G, Goffredo V *et al.* Sorafenib (BAY 43–9006) in hepatocellular carcinoma patients: from discovery to clinical development. *Curr. Med. Chem.* 19(7), 938–944 (2012).
- 20 Roses RE, Vauthey JN. Transplantation or resection for hepatocellular carcinoma: biology determines outcome. *Oncology (Williston Park)* 25(8), 760–761 (2011).
- 21 Delis SG, Bakoyiannis A, Tassopoulos N *et al.* Hepatic resection for hepatocellular carcinoma exceeding Milan criteria. *Surg. Oncol.* 19(4), 200–207 (2010).
- 22 Kim RD, Hemming AW. Hepatocellular carcinoma: resection or transplantation. *J. Gastrointest. Surg.* 13(6), 1023–1025 (2009).
- 23 Morris-Stiff G, Gomez D, de Liguori Carino N, Prasad KR. Surgical management of hepatocellular carcinoma: is the jury still out? *Surg. Oncol.* 18(4), 298–321 (2009).
- 24 Rahman A, Assifi MM, Pedrosa FE *et al.* Is resection equivalent to transplantation for early cirrhotic patients with hepatocellular carcinoma? A meta-analysis. *J. Gastrointest. Surg.* 16(10), 1897–1909 (2012).
- 25 Scartozzi M, Baroni GS, Faloppi L *et al.* Trans-arterial chemo-embolization (TACE), with either lipiodol (traditional TACE) or drug-eluting microspheres (precision TACE, pTACE) in the treatment of hepatocellular carcinoma: efficacy and safety results from a large mono-institutional analysis. *J. Exp. Clin. Cancer Res.* 29, 164 (2010).
- 26 Cho YK, Rhim H, Noh S. Radiofrequency ablation versus surgical resection as primary treatment of hepatocellular carcinoma meeting the Milan criteria: a systematic review. *J. Gastroenterol. Hepatol.* 26(9), 1354–1360 (2011).
- 27 Swan RZ, Sindram D, Martinie JB, Iannitti DA. Operative microwave ablation for hepatocellular carcinoma: complications, recurrence, and long-term outcomes. *J. Gastrointest. Surg.* 17(4), 719–729 (2013).
- 28 Gage AA. History of cryosurgery. *Semin. Surg. Oncol.* 14(2), 99–109 (1998).
- 29 Weaver ML, Ashton JG, Zemel R. Treatment of colorectal liver metastases by cryotherapy. *Semin. Surg. Oncol.* 14(2), 163–170 (1998).
- 30 Iannitti DA, Heniford T, Hale J, Grundfest-Broniatowski S, Gagner M. Laparoscopic cryoablation of hepatic metastases. *Arch. Surg.* 133(9), 1011–1015 (1998).
- 31 Padma S, Martinie JB, Iannitti DA. Liver tumor ablation: percutaneous and open approaches. *J. Surg. Oncol.* 100(8), 619–634 (2009).
- 32 Schoppmeyer K, Weis S, Mossner J, Fleig WE. Percutaneous ethanol injection or percutaneous acetic acid injection for early hepatocellular carcinoma. *Cochrane Database Syst. Rev.* 3, CD006745 (2009).
- 33 Lencioni R, Cioni D, Crocetti L, Bartolozzi C. Percutaneous ablation of hepatocellular carcinoma: state-of-the-art. *Liver Transpl.* 10(2 Suppl. 1), S91–S97 (2004).
- 34 Shiina S, Yasuda H, Muto H *et al.* Percutaneous ethanol injection in the treatment of liver neoplasms. *AJR Am. J. Roentgenol.* 149(5), 949–952 (1987).
- 35 Livraghi T, Festi D, Monti F, Salmi A, Vettori C. US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. *Radiology* 161(2), 309–312 (1986).
- 36 Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. *Am. J. Gastroenterol.* 104(2), 514–524 (2009).
- 37 Shiina S, Tagawa K, Unuma T *et al.* Percutaneous ethanol injection therapy for hepatocellular carcinoma. A histopathologic study. *Cancer* 68(7), 1524–1530 (1991).
- 38 Branco F, Bru C, Vilana R, Bianchi L, Alves De Mattos A. Percutaneous ethanol injection before liver transplantation in the hepatocellular carcinoma. *Ann. Hepatol.* 8(3), 220–227 (2009).
- 39 Castroagudin JF, Delgado M, Martinez SM *et al.* Prospective histopathological analysis of hepatocellular carcinoma treated with percutaneous ethanol injection in patients on the waiting list for liver transplantation. *Trans. Proc.* 37(3), 1477–1479 (2005).
- 40 Lencioni R, Bartolozzi C, Caramella D *et al.* Treatment of small hepatocellular carcinoma with percutaneous ethanol injection. Analysis of prognostic factors in 105 western patients. *Cancer* 76(10), 1737–1746 (1995).
- 41 Di Stasi M, Buscarini L, Livraghi T *et al.* Percutaneous ethanol injection in the treatment of hepatocellular carcinoma. A multicenter survey of evaluation practices and complication rates. *Scand. J. Gastroenterol.* 32(11), 1168–1173 (1997).
- 42 Khan KN, Yatsuhashi H, Yamasaki K *et al.* Prospective analysis of risk factors for early intrahepatic recurrence of hepatocellular carcinoma following ethanol injection. *J. Hepatol.* 32(2), 269–278 (2000).
- 43 Koda M, Murawaki Y, Mitsuda A *et al.* Predictive factors for intrahepatic recurrence after percutaneous ethanol injection therapy

- for small hepatocellular carcinoma. *Cancer* 88(3), 529–537 (2000).
- 44 Shiina S, Tateishi R, Imamura M *et al.* Percutaneous ethanol injection for hepatocellular carcinoma: 20-year outcome and prognostic factors. *Liver Int.* 32(9), 1434–1442 (2012).
- 45 Ebara M, Okabe S, Kita K *et al.* Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J. Hepatol.* 43(3), 458–464 (2005).
- 46 Fartoux L, Arrive L, Andreani T *et al.* Treatment of small hepatocellular carcinoma with acetic acid percutaneous injection. *Gastroenterol. Clin. Biol.* 29(12), 1213–1219 (2005).
- 47 Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma: a meta-analysis. *J. Hepatol.* 52(3), 380–388 (2010).
- 48 Sindram D, Lau KN, Martinie JB, Iannitti DA. Hepatic tumor ablation. *Surg. Clin. North Am.* 90(4), 863–876 (2010).
- 49 Simo KA, Sereika SE, Newton KN, Gerber DA. Laparoscopic-assisted microwave ablation for hepatocellular carcinoma: safety and efficacy in comparison with radiofrequency ablation. *J. Surg. Oncol.* 104(7), 822–829 (2011).
- 50 Poon RT, Fan ST, Tsang FH, Wong J. Locoregional therapies for hepatocellular carcinoma: a critical review from the surgeon's perspective. *Ann. Surg.* 235(4), 466–486 (2002).
- 51 Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. *Arch. Surg.* 137(4), 422–426; discussion 427 (2002).
- 52 Shiina S, Tateishi R, Arano T *et al.* Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am. J. Gastroenterol.* 107(4), 569–577; quiz 578 (2012).
- 53 Francica G, Saviano A, De Sio I *et al.* Long-term effectiveness of radiofrequency ablation for solitary small hepatocellular carcinoma: a retrospective analysis of 363 patients. *Dig. Liver Dis.* 45(4), 336–341 (2013).
- 54 Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. *Cochrane Database Syst. Rev.* 2, CD003046 (2004).
- 55 Lencioni RA, Allgaier HP, Cioni D *et al.* Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 228(1), 235–240 (2003).
- 56 Shibata T, Iimuro Y, Yamamoto Y *et al.* Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology* 223(2), 331–337 (2002).
- 57 Salhab M, Canelo R. An overview of evidence-based management of hepatocellular carcinoma: a meta-analysis. *J. Cancer Res. Ther.* 7(4), 463–475 (2011).
- 58 Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. *Br. J. Surg.* 98(9), 1210–1224 (2011).
- 59 Chen MS, Li JQ, Zheng Y *et al.* A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann. Surg.* 243(3), 321–328 (2006).
- 60 Montorsi M, Santambrogio R, Bianchi P *et al.* Survival and recurrences after hepatic resection or radiofrequency for hepatocellular carcinoma in cirrhotic patients: a multivariate analysis. *J. Gastrointest. Surg.* 9(1), 62–67; discussion 67–68 (2005).
- 61 Abu-Hilal M, Primrose JN, Casaril A, McPhail MJ, Pearce NW, Nicoli N. Surgical resection versus radiofrequency ablation in the treatment of small unifocal hepatocellular carcinoma. *J. Gastrointest. Surg.* 12(9), 1521–1526 (2008).
- 62 Liang HH, Chen MS, Peng ZW *et al.* Percutaneous radiofrequency ablation versus repeat hepatectomy for recurrent hepatocellular carcinoma: a retrospective study. *Ann. Surg. Oncol.* 15(12), 3484–3493 (2008).
- 63 Huang J, Yan L, Cheng Z *et al.* A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann. Surg.* 252(6), 903–912 (2010).
- 64 Feng K, Yan J, Li X *et al.* A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J. Hepatol.* 57(4), 794–802 (2012).
- 65 Pompili M, Saviano A, De Matthaeis N *et al.* Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤ 3 cm. Results of a multicenter Italian survey. *J. Hepatol.* 59(1), 89–97 (2013).
- 66 Iannitti DA, Martin RC, Simon CJ *et al.* Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. *HPB (Oxford)* 9(2), 120–124 (2007).
- 67 Swan R, Tsirlina V, Sindram D, Martinie JB, Iannitti DA. Fundamentals of microwave physics: application to hepatic ablation. *J. Microwave Surg.* 30, 25–40 (2012).
- 68 Boutros C, Somasundar P, Garrean S, Saied A, Espat NJ. Microwave coagulation therapy for hepatic tumors: review of the literature and critical analysis. *Surg. Oncol.* 19(1), e22–e32 (2010).
- 69 Lu MD, Chen JW, Xie XY *et al.* Hepatocellular carcinoma: US-guided percutaneous microwave coagulation therapy. *Radiology* 221(1), 167–172 (2001).
- 70 Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. *Oncology* 62(Suppl. 1), 64–68 (2002).
- 71 Dong B, Liang P, Yu X *et al.* Percutaneous sonographically guided microwave coagulation therapy for hepatocellular carcinoma: results in 234 patients. *AJR Am. J. Roentgenol.* 180(6), 1547–1555 (2003).
- 72 Dong BW, Liang P, Yu XL *et al.* Long-term results of percutaneous sonographically-guided microwave ablation therapy of early-stage hepatocellular carcinoma. *Zhonghua Yi Xue Za Zhi* 86(12), 797–800 (2006).
- 73 Liang P, Dong B, Yu X *et al.* Prognostic factors for survival in patients with hepatocellular carcinoma after percutaneous microwave ablation. *Radiology* 235(1), 299–307 (2005).
- 74 Morita T, Shibata T, Okuyama M *et al.* Microwave coagulation therapy for liver metastases from colorectal cancer. *Gan To Kagaku Ryoho* 31(5), 695–699 (2004).
- 75 Simon CJ, Dupuy DE, Iannitti DA *et al.* Intraoperative triple antenna hepatic microwave ablation. *AJR Am. J. Roentgenol.* 187(4), W333–W340 (2006).
- 76 Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. *Ann. Surg. Oncol.* 17(1), 171–178 (2010).
- 77 Pacella CM, Bizzarri G, Francica G *et al.* Analysis of factors predicting survival in patients with hepatocellular carcinoma treated with percutaneous laser ablation. *J. Hepatol.* 44(5), 902–909 (2006).
- 78 Pacella CM, Francica G, Di Lascio FM *et al.* Long-term outcome of cirrhotic patients with early hepatocellular carcinoma treated with ultrasound-guided percutaneous laser ablation: a retrospective analysis. *J. Clin. Oncol.* 27(16), 2615–2621 (2009).

- 79 Davalos RV, Mir IL, Rubinsky B. Tissue ablation with irreversible electroporation. *Ann. Biomed. Eng.* 33(2), 223–231 (2005).
- 80 Sugar IP, Neumann E. Stochastic model for electric field-induced membrane pores. *Biophys. Chem.* 19(3), 211–225 (1984).
- 81 Freeman SA, Wang MA, Weaver JC. Theory of electroporation of planar bilayer membranes: predictions of the aqueous area, change in capacitance, and pore-pore separation. *Biophys. J.* 67(1), 42–56 (1994).
- 82 Lee EW, Wong D, Prikhodko SV *et al.* Electron microscopic demonstration and evaluation of irreversible electroporation-induced nanopores on hepatocyte membranes. *J. Vasc. Interv. Radiol.* 23(1), 107–113 (2012).
- 83 Rubinsky B, Onik G, Mikus P. Irreversible electroporation: a new ablation modality – clinical implications. *Technol. Cancer Res. Treat.* 6(1), 37–48 (2007).
- 84 Lee MH, Lee WH, Van Y, Contag CH, Liu CP. Image-guided analyses reveal that non-CD4⁺ splenocytes contribute to CD4⁺ T cell-mediated inflammation leading to islet destruction by altering their local function and not systemic trafficking patterns. *Mol. Imaging* 6(6), 369–383 (2007).
- 85 Charpentier KP, Wolf F, Noble L, Winn B, Resnick M, Dupuy DE. Irreversible electroporation of the liver and liver hilum in swine. *HPB (Oxford)* 13(3), 168–173 (2011).
- 86 Lencioni R, Izzo F, Crocetti L *et al.* A prospective, multicenter Phase II clinical trial using irreversible electroporation for the treatment of early stage HCC. *J. Vasc. Interv. Radiol.* 23(8), 1114 (2012).
- 87 Bower M, Sherwood L, Li Y, Martin R. Irreversible electroporation of the pancreas: definitive local therapy without systemic effects. *J. Surg. Oncol.* 104(1), 22–28 (2011).
- 88 Martin RC 2nd, McFarland K, Ellis S, Velanovich V. Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival. *Ann. Surg. Oncol.* doi:10.1245/s10434-012-2736-1 (2012) (Epub ahead of print).
- 89 Martin RC 2nd, McFarland K, Ellis S, Velanovich V. Irreversible electroporation therapy in the management of locally advanced pancreatic adenocarcinoma. *J. Am. Coll. Surg.* 215(3), 361–369 (2012).
- 90 Haar GT, Coussios C. High intensity focused ultrasound: physical principles and devices. *Int. J. Hyperthermia* 23(2), 89–104 (2007).
- 91 Zhang L, Zhu H, Jin C *et al.* High-intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins. *Eur. Radiol.* 19(2), 437–445 (2009).
- 92 Guglielmi A, Ruzzenente A, Valdegamberi A *et al.* Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. *J. Gastrointest. Surg.* 12(1), 192–198 (2008).
- 93 Sindram D, Swan RZ, Lau KN, McKillop IH, Iannitti DA, Martinie JB. Real-time three-dimensional guided ultrasound targeting system for microwave ablation of liver tumours: a human pilot study. *HPB (Oxford)* 13(3), 185–191 (2011).
- 94 Sindram D, McKillop IH, Martinie JB, Iannitti DA. Novel 3-D laparoscopic magnetic ultrasound image guidance for lesion targeting. *HPB (Oxford)* 12(10), 709–716 (2010).
- 95 Peng ZW, Zhang YJ, Chen MS *et al.* Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. *J. Clin. Oncol.* 31(4), 426–432 (2013).

■ Websites

- 101 ClinicalTrials.gov. Effectiveness of microwave ablation of hepatocellular carcinoma as compared to radiofrequency ablation. <http://clinicaltrials.gov/ct2/show/NCT01340105?term=NCT01340105&rank=1>
- 102 ClinicalTrials.gov. Pilot study of irreversible electroporation (IRE) to treat early-stage primary liver cancer (HCC). <http://clinicaltrials.gov/ct2/show/NCT01078415?term=NCT01078415&rank=1>